GLYCOGEN SYNTHASE KINASE-3 INHIBITORS

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to novel conjugates for inhibiting glycogen synthase kinase-3 (GSK-3) and their use in regulating biological conditions mediated by GSK-3 activity and, more particularly, to the use of such conjugates in the treatment of biological conditions such as type II diabetes, neurodegenerative disorders and diseases and affective disorders. The present invention further relates to methods of treating affective disorders using GSK-3 inhibitors.

Protein kinases, the enzymes that phosphorylate protein substrates, are key players in the signaling of extracellular events to the cytoplasm and the nucleus, and take part in practically any event relating to the life and death of cells, including mitosis, differentiation and apoptosis. As such, protein kinases have long been favorable drug targets. However, since the activity of protein kinases is crucial to the well being of the cell, while their inhibition oftentimes leads to cell death, their use as drug targets is limited. Although cell death is a desirable effect for anticancer drugs, it is a major drawback for most other therapeutics.

Glycogen synthase kinase-3 (GSK-3), a member of the protein kinases family, is a cytoplasmic serine-threonine kinase that is involved in insulin signaling and metabolic regulation, as well as in Wnt signaling and the scheme of cell fate during embryonic development. Two similar isoforms of the enzyme, termed GSK-3α and GSK-3β, have been identified.

GSK-3 has long been considered as a favorable drug target among the protein kinase family since unlike other protein kinases, which are typically activated by signaling pathways, GSK-3 is normally activated in resting cells, and its activity is attenuated by the activation of certain signaling pathways such as those generated by the binding of insulin to its cell-surface receptor. Activation of the insulin receptor leads to the activation of protein kinase B (PKB, also called Akt), which in turn phosphorylates GSK-3, thereby inactivating it. The inhibition of GSK-3 presumably leads to the activation of glycogen synthesis. The intricate insulin-signaling pathway is further complicated by negative-feedback regulation of insulin signaling by GSK-3 itself, which phosphorylates insulin-receptor substrate-1 on serine residues (Eldar-Finkelman et al., 1997).